REPORT

Mutations in *DOCK7* in Individuals with Epileptic Encephalopathy and Cortical Blindness

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Epileptic encephalopathies are increasingly thought to be of genetic origin, although the exact etiology remains uncertain in many cases. We describe here three girls from two nonconsanguineous families affected by a clinical entity characterized by dysmorphic features, early-onset intractable epilepsy, intellectual disability, and cortical blindness. In individuals from each family, brain imaging also showed specific changes, including an abnormally marked pontobulbar sulcus and abnormal signals (T2 hyperintensities) and atrophy in the occipital lobe. Exome sequencing performed in the first family did not reveal any gene with rare homozygous variants shared by both affected siblings. It did, however, show one gene, *DOCK7*, with two rare heterozygous variants (c.2510delA [p.Asp837Alafs*48] and c.3709C>T [p.Arg1237*]) found in both affected sisters. Exome sequencing performed in the proband of the second family also showed the presence of two rare heterozygous variants (c.983C>G [p.Ser328*] and c.6232G>T [p.Glu2078*]) in *DOCK7*. Sanger sequencing confirmed that all three individuals are compound heterozygotes for these truncating mutations in *DOCK7*. These mutations have not been observed in public SNP databases and are predicted to abolish domains critical for DOCK7 function. *DOCK7* codes for a Rac guanine nucleotide exchange factor that has been implicated in the genesis and polarization of newborn pyramidal neurons and in the morphological differentiation of GABAergic interneurons in the developing cortex. All together, these observations suggest that loss of *DOCK7* function causes a syndromic form of epileptic encephalopathy by affecting multiple neuronal processes.

Epileptic encephalopathies (EEs) are a heterogeneous group of severe disorders that are characterized by seizures and abundant epileptiform activity and contribute to cognitive and behavioral impairment.[1] Genetics is believed to play a major role in these conditions. Although current observations suggest the involvement of hundreds of genes in EE, their identity has only been elucidated in a small proportion of cases.[2] Moreover, genes whose mutations are known to cause EE are typically associated with variable and overlapping phenotypes, complicating the establishment of etiological diagnoses in clinical settings. Although EE-causing mutations in several genes have been shown to affect metabolic pathways or ion-channel function, other genes found to be mutated in EE are specifically associated with the regulation of developmental processes, including the proliferation of neuronal progenitors, the differentiation and migration of neurons, and the elaboration of neuronal circuits. Very little is known about the identity and mechanisms of action of these EE-associated developmental genes. We describe here two unrelated families affected by a specific condition characterized by EE, cortical blindness, dysmorphic features, and specific structural brain abnormalities. Using exome sequencing, we identified mutations in *DOCK7*, a regulator of neuronal development, in the two families, providing insight into the pathophysiology of EE.

This study was approved by the ethics committees of the participating institutions, and informed consent was obtained from each participant or legal guardian. The first family (family A), consisting of two affected female siblings (A-1 and A-2) born to nonconsanguineous healthy French Canadian parents, was recruited at Sainte-Justine Hospital (Montreal). Individuals A-1 and A-2 are currently 7 and 5 years old, respectively. They were born at term after unremarkable pregnancy and delivery. Their neonatal course was uneventful, but in individual A-1, the discovery of a heart murmur led to a diagnosis of aortic supravalvular stenosis and bicuspid valve, for which the child was operated on at 4 months of age. Echocardiography was normal in individual A-2.

Both sisters presented with tonic seizures between 2 and 4 months of age. At 1 year of age, individual A-1 displayed infantile spasms, which disappeared with the administration of adrenocorticotropic hormone, whereas individual

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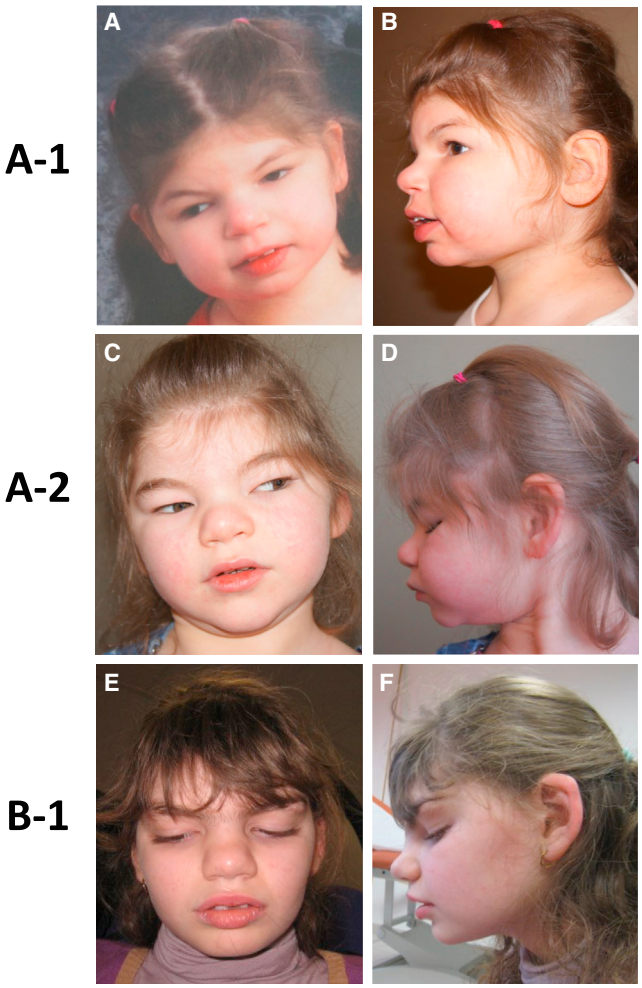

Figure 1. Pictures of Individuals with Mutations in *DOCK7*
Frontal and profile photos of the faces of affected individuals from families A (A-1 and A-2) and B (B-1). These individuals display similar dysmorphic features, including a low anterior hairline, periorbital fullness, telecanthus, a broad nasal tip, and anteverted nares.

A-2 started to show myoclonus, which occurred as many as 50 times a day. Over the following months, individual A-2 started to show different types of seizures, including myoclonus, partial complex seizures with rotation of the head, drop attacks, and tonic seizures. Control was poor in both sisters despite the administration of multiple antiepileptic drugs in various combinations and several trials with the ketogenic diet. Electroencephalography (EEG) performed at 11 months of age in individual A-1 showed a pattern consistent with hypsarrhythmia, whereas EEG performed at 2 months of age in individual A-2 showed epileptic activity in the left posterior quadrant and in the right temporoparietal region. Subsequent EEG studies showed multifocal epileptic activity in both sisters.

Parents noticed a lack of attentiveness to visual stimuli in their children during the first few months of life. Ophthalmological examinations showed normal eye movements, pupillary reaction, and fundus in both sisters, consistent with a diagnosis of cortical blindness. Progressive improvement over the following years was noted. Currently, individual A-1 displays grossly normal visual pursuit, although she has more difficulty following objects in the upper visual fields, whereas individual A-2 can now follow a moving object, but she does not see well enough to play with toys.

Individual A-1 started to walk at 20 months of age, but her gross motor skills deteriorated over the last few years. She can now get up by herself but cannot walk without help. She cannot eat by herself. She does not point or use her hands to communicate. She can hit objects against each other. She does not speak, but she can understand a few simple commands. She can smile, but not in a social context. She displays limited visual contact. Overall, her nonverbal interactions are suggestive of autism. Individual A-2 began walking at 28 months of age. Currently, she can run but cannot jump in place. She can eat with a spoon and has a pincer grasp but cannot point to objects. She can say about 30 words and associate two words. She can designate body parts on demand and understand simple commands.

The occipitofrontal circumference (OFC) of individual A-1 was 45 cm (tenth percentile) at 19 months of age, whereas that of individual A-2 was 42.2 cm (tenth percentile) at 8 months of age. Both sisters showed similar facial features, including a low anterior hairline, some periorbital fullness, telecanthus, and a broad nasal tip with anteverted nares (Figures 1A and 1B). Neurological examination was unremarkable in both of them.

Karyotyping was normal in both siblings. In addition, array genomic hybridization (105K-feature whole-genome microarray, Signature Genomic Laboratories) did not show any abnormality in individual A-2. Mutation analysis of *MECP2* (MIM 300005) and *CDKL5* (MIM 300203) in individual A-1 and a methylation study of the region associated with Angelman syndrome (MIM 105830) in individual A-2 were unremarkable. A metabolic work-up, including plasma amino acid and urine organic acid chromatography, was normal in both sisters. Brain MRI performed at 25 months of age in individual A-1 showed an abnormally marked pontobulbar sulcus associated with mild pontine hypoplasia, a thin and short corpus callosum, and abnormal signals (T2 hyperintensities) and atrophy in the white and gray matter of the occipital region (Figures 2A, 2C, 2D, 2F, 2G, 2I, 2K, and 2M). Brain MRI performed at 8 months of age in individual A-2 showed mild hypoplasia of the corpus callosum according to the report of the radiologist who interpreted the images. These images were not available for review. Brain spectroscopy revealed normal creatine, *N*-acetylaspartic acid, and choline levels in both sisters.

The exomes of these affected individuals (A-1 and A-2) were captured from blood genomic DNA with the use of Agilent SureSelect Human All Exon Kit V4 and were sequenced (2 × 100 bp, three exomes per lane) with the Illumina HiSeq2000 at the McGill University and Genome Quebec Innovation Center (Montreal). Sequence

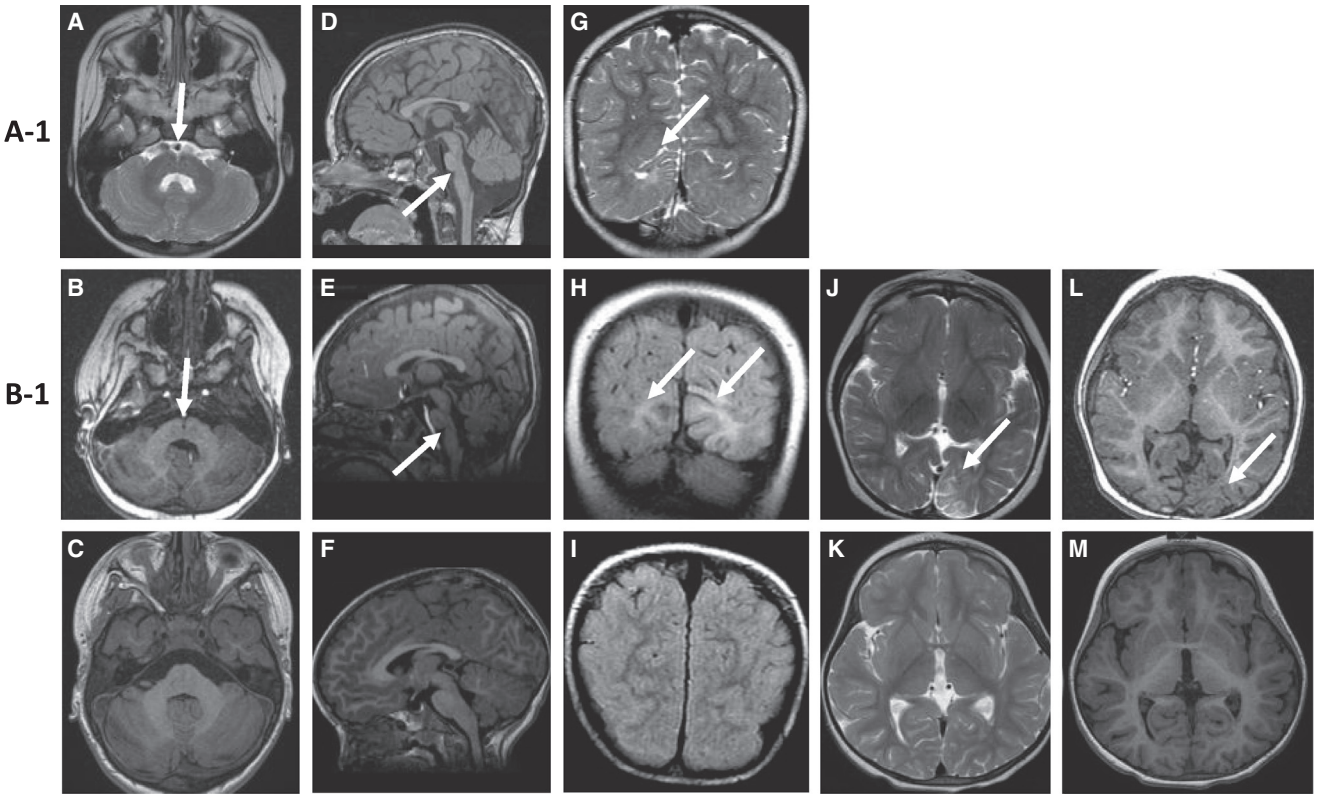

Figure 2. Brain MRI of Individuals with Mutations in *DOCK7*
MRI was performed at 2 years of age in individuals A-1 (A, D, and G) and B-1 (B, E, H, J, and L) and a control individual who was also matched for sex (C, F, I, K, and M) by means of the following modalities: axial T2 (A, J, and K), axial T1 (B, C, L, and M), sagittal T1 (D–F), coronal T2 (G), and coronal FLAIR (H and I).
(A–F) Abnormally marked pontobulbar sulcus (white arrows) and mild pontine hypoplasia in individuals A-1 (A and D) and B-1 (B and E). See the control individual in (C) and (F) for comparison.
(G–K) Hypersignal and atrophy in the occipital cortex (white arrows), including in the regions lining the calcarine sulcus, in individual A-1 (G). See the control individual in (I) and (K) for comparison.
(L and M) Dedifferentiation of the occipital cortex and white matter with a sequellae aspect in individual B-1 (L). See the control individual in (M) for comparison.

processing, alignment (with the Burrows-Wheeler Aligner), and variant calling were done with the Broad Institute Genome Analysis Toolkit (GATK v.4) and annotated with ANNOVAR.[3] The average exome coverage of the target bases was 121× (A-1) and 141× (A-2), and 99% of the target region was covered by at least ten reads. In view of the likely autosomal-recessive mode of inheritance in this family, we only considered well-covered variants (≥10×) that were shared by both affected sisters. We next filtered out (1) synonymous or intronic variants other than those affecting the consensus splice sites, (2) variants seen in more than 1% of an in-house exome data set (n = 600) from unrelated projects, and (3) variants with a minor allele frequency greater than 0.5% in either 1000 Genomes or the NHLBI Exome Sequencing Project Exome Variant Server (EVS). This filtering strategy resulted in a total of 154 variants shared by both sisters, and none of them affected genes associated with intellectual disability (ID) or epilepsy. None of these variants were homozygous. Only one gene, *DOCK7*, showed multiple heterozygous variants (c.3709C>T [p.Arg1237*] [RefSeq accession number NM_001271999.1, chr1:62995020G>A] and c.2510delA [p.Asp837Alafs*48] [chr1:63021582T>delT]; UCSC Genome Browser hg19 assembly) shared by both sisters. Sanger sequencing showed that both sisters are compound heterozygotes for these mutations (Figure 3A).

The second family (B) was referred to the Department of Genetics of Hôpital Necker – Enfants Malades (Paris) because of congenital blindness in the first of three daughters born to nonconsanguineous healthy French parents. The affected individual (B-1), who is currently 10 years old, was born at term after an unremarkable delivery. The initial course was uneventful until the parents noticed the absence of visual contact in the infant. Ophthalmologic examination performed at the age of 6 months showed the absence of ocular reaction to visual threat, normal pupillary reflex, and normal aspect of the fundus. Evoked visual potentials were unremarkable, but electroretinographic (ERG) traces were ambiguous. Ophthalmological examinations repeated at 2 and 9 years of age showed unchanged retinal aspect and normal ERG traces, leading to the diagnosis of cortical blindness. Currently, at age 10, she shows wandering eye movements and a complete absence of reaction to visual threat and light stimulation.

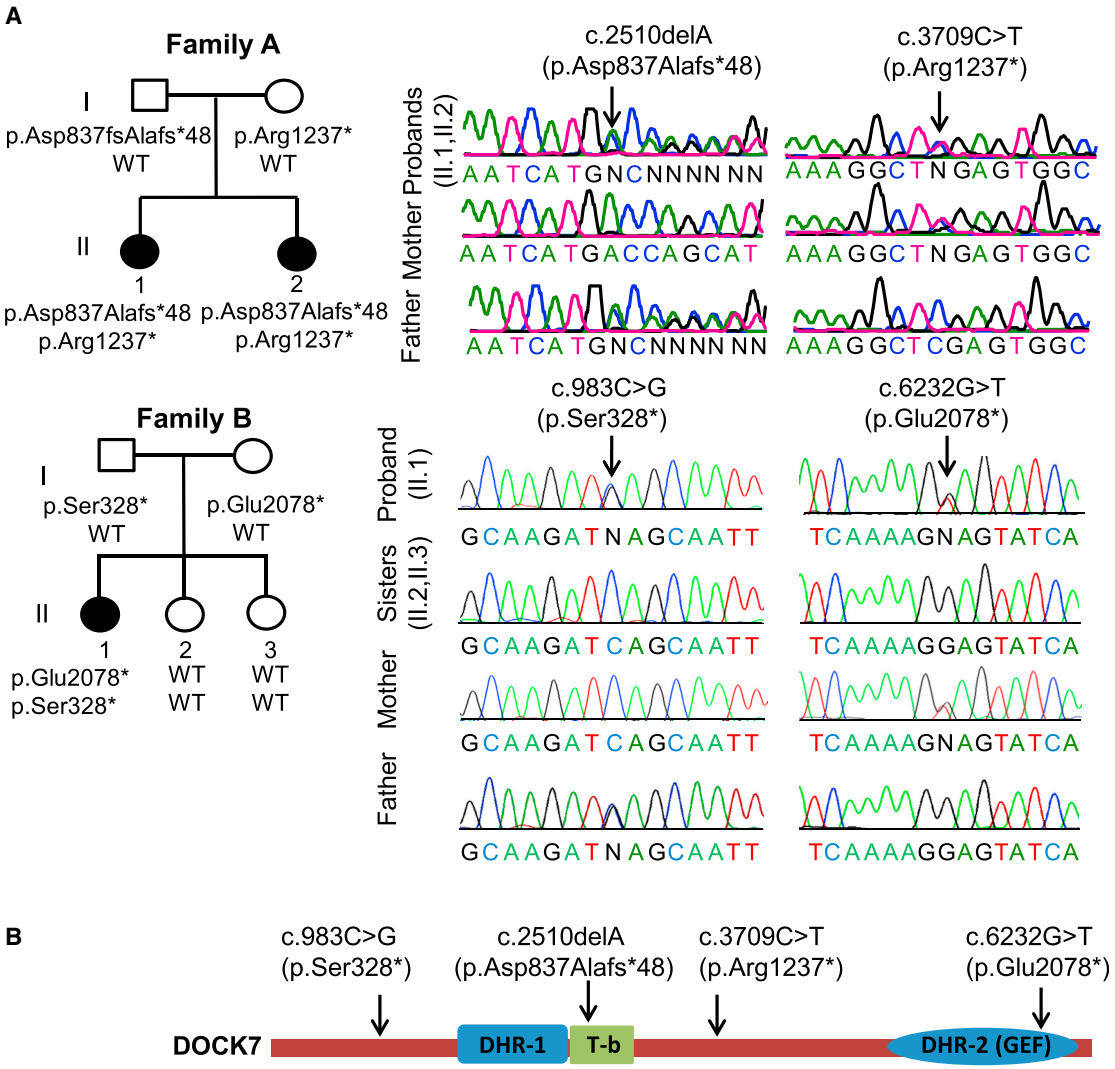

Figure 3. Truncating Mutations in *DOCK7* in Individuals with EE and Cortical Blindness
(A) Pedigrees of the two families affected by *DOCK7* mutations and chromatograms of these mutations.
(B) A schematic of DOCK7 (2,129 amino acids) shows its DOCK homology domains, DHR-1 (amino acids 516–727) and DHR-2 (amino acids 1,668–2,110), as well as the TACC3-binding region (T-b) and the relative amino acid positions of the identified alterations. Nucleotide and amino acid positions are based on RefSeq NM _001271999.1 and NP_001258928.1, respectively. Locations of the DHR-1 and DHR-2 domains are based on DOCK7 UniProt prediction (accession number Q96NS7, isoform 2), and the positions of the T-b boundaries are based on Yang et al.[4]

Seizures were first noticed at 6 months of age and were initially characterized by eye revulsion and rhythmic arm and body movements. Initial EEG recordings performed at the age of 7.5 months showed left occipital epileptic activity. Subsequently, she showed short absences with immobility, moderate body sagging, and unreactiveness to external stimuli. EEG recordings at 2–3 years of age showed multifocal epileptic activity associated with occasional electroclinical spasms. Currently, despite the administration of various antiepileptic drugs alone or in combination, she experiences repeated tonic-clonic seizures.

The psychomotor development of individual B-1 was initially unremarkable except for the presence of moderate hypotonia. She started to walk at 22 months of age, but she did not acquire any new skills thereafter. She can walk without help in known environments. Her speech skills are limited to repeating the last three words of sentences that she hears. She understands simple commands. She can smile, but not in a social context. She uses her hands to grasp objects, but not to point or communicate. She can bring a spoon to her mouth, but she is unable to eat by herself. She manifests hand, trunk, and head (screwing and unscrewing movements) stereotypies.

Since the neonatal period, her weight and size have been on +2–3 SDs, contrasting with an OFC on −1 SD. She exhibits dysmorphic facial features, including bitemporal narrowness, a low anterior hairline, thick and duplicated eyebrows, synophrisis, long eyelashes, enophthalmia, a large and prominent nasal root, a bulbous nasal tip, a thick and hammered helix, thick earlobes, a short philtrum, full lips and an everted lower lip, and spaced incisors (Figures 1E and 1F). Currently, her neurological exam is

unremarkable. Karyotyping at a resolution of 400 bands was normal. In addition, array genomic hybridization (Affimetrix Cytogenetics Whole-Genome 2.7M Array) did not show any de novo abnormality in individual B-1.

Brain MRI performed at the age of 2 years showed an abnormally marked pontobulbar sulcus, mild pontine hypoplasia, and abnormal signals (T2 hyperintensities) with atrophy in the occipital white and gray matter (Figures 2B, 2C, 2E, 2F, and 2H–2M).

The exome of proband B-1 was captured from blood genomic DNA with the use of the SureSelect Human All Exon Kit V3 (Agilent) and sequenced (2 × 75 bp) with the Illumina HiSeq2000 system at the Genomic Core Facility of Institut Imagine (Paris). Sequences were aligned to the human genome reference sequence (UCSC Genome Browser hg19 assembly), and SNPs were called on the basis of allele calls and read depth with the use of the Consensus Assessment of Sequence and Variation pipeline (v.1.8, Illumina). Genetic-variation annotation was performed by an in-house pipeline. The average exome coverage of the target bases was 78×, and 88% of the target region was covered by at least 15 reads. Only the variants whose positions were covered ≥10× were further considered.

The filtering strategy used for analyzing the exome of individual B-1 was the same as that described above. On the basis of our finding in family A, we also hypothesized an autosomal-recessive mode of inheritance in family B and focused our attention on homozygous and multiple heterozygous variants. In total, nine variants (one homozygous and eight heterozygous variants) in five genes met these criteria, and none of them affected genes known to be associated with ID or epilepsy (Table S1, available online). Among these variants, we identified two heterozygous truncating mutations in *DOCK7*: c.983C>G (p.Ser328*) (chr1:63100496G>C) and c.6232G>T (p.Glu2078*) (chr1:62923324C>A, RefSeq NM_001271999.1, UCSC Genome Browser hg19 assembly). Sanger sequencing showed that individual B-1 is a compound heterozygote for these mutations and that her two unaffected siblings do not carry any of them (Figure 3A).

None of the four *DOCK7* mutations identified in families A and B have been previously reported in any public SNP database (1000 Genomes, dbSNP, or the NHLBI EVS). We also searched our in-house database of 1,500 similarly sequenced exomes, including 200 exomes from French Canadians, and we did not identify any of these four mutations or any other truncating or splicing ones in *DOCK7*. Moreover, inspection of *DOCK7* for loss-of-function (splicing, nonsense, and frameshift) variants in the NHLBI EVS revealed only two heterozygous truncating variants, in two different individuals, out of approximately 13,000 alleles from individuals with European American and African American ancestry. These observations indicate that DOCK7, despite its large size (2,129 amino acids), does not accumulate loss-of-function-variants in the general population, suggesting that its disruption might be detrimental in humans. We further used Sanger sequencing to screen the coding exons and flanking intronic regions of *DOCK7* (Table S2) in 35 EE-affected individuals with burst suppression (n = 18/35); infantile migrating partial seizures and no mutations in *KCNT1* (MIM 608167), *SNC1A* (MIM 182389), *PLBC1*, *TBC1D24* (MIM 613577), or *SLC25A22* (MIM 609302) (n = 11/35); or Rett-like syndrome (MIM 312750) and no mutations in *MECP2* or *CDKL5* (n = 6/35). We identified polymorphisms, but no candidate single heterozygous or biallelic mutations, in these individuals (Table S3).

DOCK7 is a member of the DOCK180-related protein superfamily, which emerged as a distinct class of guanine nucleotide exchange factors (GEFs) for Rac and/or Cdc42 GTPases.[5] Like other DOCK180-related proteins, DOCK7 is characterized by the presence of a DHR1 domain, which is predicted to bind phospholipids and thus facilitate recruitment to the plasma membrane, and of a catalytic DHR2 domain, which positively regulates Rac and Cdc42 by promoting the exchange of GDP for GTP.[6,7] The mutations identified in both families affect all the major *DOCK7* isoforms and are located in upstream exons, indicating that they have the potential to induce nonsense-mediated decay of the corresponding mRNAs.[8] These mutations are also predicted to abolish the conserved domains of DOCK7 and are thus likely to cause a loss of its function (Figure 3B).

The individuals described here show a similar phenotype, characterized by intractable seizures, ID, and cortical blindness. At least two of them also share distinctive brain MRI changes characterized by a strikingly marked pontobulbar sulcus and abnormal MRI signals with atrophy in the occipital lobe. Moreover, these individuals show similar dysmorphic features, including a low anterior hairline, periorbital fullness, telecanthus, a broad nasal tip, and anteverted nares. The identification of multiple rare and deleterious mutations in *DOCK7* in unrelated individuals with such a unique phenotype strongly suggests that it is the causal gene.

DOCK7 is located in all major regions of the brain, including the cortex and hippocampus, from early embryonic to postnatal stages and is present in lower amounts in adulthood.[4] Knockdown experiments performed in vitro and in vivo showed that DOCK7 regulates neurogenesis by promoting the differentiation of progenitors into neurons.[4] During the cell cycle, the nuclei of neuronal progenitors migrate between the apical and basal aspects of the ventricular zone. DOCK7 influences neuronal differentiation by impeding basal-to-apical interkinetic nuclear migration. This leads to extended residency of progenitors at the basal aspect of the ventricular zone, resulting in ectopic mitoses, which are more likely to generate neurons than self-renewing progenitors. DOCK7 exerts its effect by directly antagonizing the microtubule-growth-promoting function of the centrosome-associated protein TACC3 in a GEF-independent fashion. DOCK7 interaction with TACC3 is mediated by a protein region that is located

between the DHR1 and DHR2 domains. Importantly, other DOCK-180 family members do not compensate for this function of DOCK7, given that knockdown of *DOCK7* alone is sufficient to cause defects in neurogenesis.

DOCK7 is also required for the regulation of neuronal polarity. It promotes the development of nascent axons by activating Rac1, which leads to the phosphorylation and inactivation of the microtubule-destabilizing protein Op18.[6] In contrast to its role in neurogenesis, this function of DOCK7 is thus mediated by its GEF activity. Recruitment of DOCK7 at the plasma membrane via the binding of DHR1 to PtdIns(3,4,5)P_3 also appears to be important for its function in axonal development.[6] Interestingly, in vivo expression of *DOCK7* in the developing cortex results in the accumulation of multipolar neurons that show impaired migration.[4] All together, these observations indicate that DOCK7 is an important regulator of microtubule assembly both in the context of neurogenesis and in the establishment of neuronal polarity.

In addition to playing a role in prospective pyramidal neurons, DOCK7 also controls the development of GABAergic interneurons. DOCK7 is present in chandelier cells, a subtype of cortical interneurons that have powerful control over the output of pyramidal neurons.[9] Knockdown of mouse ortholog *Dock7* causes a reduction of the number and size of synaptic boutons formed by these cells. DOCK7 controls the development of chandelier cells by physically interacting with the receptor tyrosine kinase ERBB4 and enhancing its activation and does so independently of its GEF activity.[9] Interestingly, *ERBB4* (MIM 600543) haploinsufficiency has been described in individuals with EE or moderate ID.[10,11] Collectively, these observations indicate that DOCK7 exerts distinct roles in different cell types during brain development by interacting with a variety of protein complexes. Two spontaneous truncating alleles of *Dock7* have been characterized in mice.[12] These mutants show hypopigmentation, but no gross behavioral abnormalities, in paradigms probing anxiety and stress-related behavior. Assessing the impact of *Dock7* disruption on cortical function in these mice would require extended testing of specific cognitive paradigms.

The function of cortical networks depends on an exquisite balance between synaptic excitatory and inhibitory activities, respectively mediated by glutamatergic pyramidal cells and GABAergic interneurons.[13] Indeed, alterations of GABAergic cell function, either during development or in the mature brain, can cause increased excitability and epilepsy. The intractable seizures observed in all three affected individuals described here could thus result from the abnormal development of the GABAergic network associated with the loss of DOCK7 function. Another prominent feature observed in these individuals is the presence of cortical blindness, which is typically caused by altered sensory processing within cortical areas in the occipital lobes. The early onset of the visual impairment in our affected individuals and its stability or improvement later in life suggest that it resulted from a developmental process. Interestingly, in at least two of the individuals, brain MRI showed abnormal signals (T2 hyperintensities) and atrophy in the occipital cortex, including in regions lining the calcarine sulcus, where the primary visual cortex is localized. These signal abnormalities might represent altered axonal or myelin integrity resulting in visual impairment. Although these changes are typically associated with sequellae of vascular or inflammatory insults, the mechanism underlying their development in the context of the genetic condition described here is uncertain. The individuals described here also display an abnormally marked pontobulbar sulcus and mild pontine hypoplasia, which should alert clinicians to the disorder described here and to a potential involvement of *DOCK7*.

In summary, we have described a neurodevelopmental condition that is causally linked to recessive mutations in *DOCK7*. This condition is characterized by specific clinical features, which should make it readily recognizable by clinicians. Our work also suggests that pathways involved in microtubule assembly and chandelier cell development contribute to the pathogenesis of EE.

Supplemental Data

Supplemental Data include three tables and can be found with this article online at http://dx.doi.org/10.1016/j.ajhg.2014.04.012.

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Web Resources

The URLs for data presented herein are as follows:

1000 Genomes Project, http://browser.1000genomes.org/
dbSNP, http://www.ncbi.nlm.nih.gov/projects/SNP/

Ensemble Genome Browser, http://www.ensembl.org

GATK Best Practices, http://www.broadinstitute.org/gatk/guide/topic?name=best-practices

NHLBI Exome Sequencing Project (ESP) Exome Variant Server, http://evs.gs.washington.edu/EVS/

Online Mendelian Inheritance in Man (OMIM), http://www.omim.org

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